REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants have canceled claims 21 and 22 and added new claims 23 through 26. Antecedent basis for the new claims may be found in the specification on page 7, lines 13 to 17, page 11, lines 1 through 10, and on page 19, line 12 through page 28, line 19. Thus claims 1 through 15, 18 through 20 and 23 through 26 are now in the case and are presented for examination.

Applicants have amended claim 1 to make it clear that the amount of N-acetyl-L-methionine employed in excess of the amount of N-acetyl-seleno-L-methionine is sufficient to suppress uptake of the N-acetyl-seleno-L-methionine into body tissues. See page 6, lines 4 through 15 of the specification for antecedent basis. Applicants have amended claim 3 to make it clear that it is the mass ratio of N-acetyl-l-methionine to N-acetyl-seleno-L-methionine that is 20:1 to 300:1. See page 7, lines 13 to 17 of the specification for antecedent basis. Applicants have also corrected some minor informalities in claims 9 and 15. Thus claim 3 is longer indefinite and no rejection of the claim should be maintained under 35 USC 112, second paragraph. Applicants have amended claim 18 to make it clear that the administration of the composition is efficacious against tumors because the composition suppresses angiogenic activity of the

tumors. See page 5, lines 7 to 14 of the specification for antecedent basis.

The Examiner has found three new prior art references from the literature and has combined these references as secondary references together with US Patent 5,006,551 to GROKE et al to argue that all of the Applicants' claims cover obvious subject matter under 35 USC 103. Lastly the Examiner argues that the presently claimed invention is so similar to the invention disclosed and claimed in US Patent 5,006,551 that the present Applicants must file a terminal disclaimer disclaiming the terminal portion of any patent that may issue here beyond the expiration date of US Patent 5,006,551.

Applicants are claiming compositions that are a significant improvement over the compositions disclosed in US Patent 5,006,551 to GROKE et al so that this patent per se provides no basis for the Examiner to argue that the claims now presented cover obvious subject matter. In addition Applicants do not believe that the Examiner's combination of US Patent 5,006,551 with the three newly cited secondary references, namely, MILLIS et al, MENTER et al, and BOMMARIUS et al provides a solid basis for the Examiner to reject any claim now presented as covering obvious subject matter.

The Examiner argues that MILLIS et al discloses some experimental data that N-acetyl-L-methionine, supplemented with L-arginine, inhibits growth of a subcutaneously transplanted Morris heptanoma in the absence of cachexia. MILLIS et al obtained the data after feeding rats a diet including a mixture of essential amino acids, but where the amounts of L-Met and L-Arg were varied from the norm to measure the effects on the test rats. The L-Met was replaced by the more stable N-acetyl-L-methionine, less subject to degradation because of the N-acetyl group and the L-Arg concentration was varied. However, this reference in no way suggests the presently claimed invention especially since the Applicants do not include L-Arg in their compositions, and there is no indication in the reference that the N-acetyl-L-methionine is per se an effective anti-cancer compound.

Next the Examiner has cited the MENTER et al reference which he maintains discloses that L-selenomethionine (SeMet) is an anti-cancer compound. Structurally L-selenomethionine differs from the Applicants' N-acetyl-seleno-L-methionine in that the L-seleno methionine has no N-acetyl group; that is the N-acetyl group is replaced by hydrogen, so that the L-seleno methionine has a primary amino group (free amino group) instead of an N-acetyl-amino group. In addition in the MENTER et al reference when the SeMet was compared in terms of its anti-tumor activity with a different selenium-containing compound, namely, sodium selenite, the sodium

selenite proved to have significantly superior anti-tumor activity, and so, one skilled in the art reading this reference, would not be motivated to employ an organic Se-containing selenium, such as the SeMet, let alone N-acetyl-seleno-L-methionine, in the treatment of tumors when the sodium selenite appeared to be much more promising.

Furthermore when Applicants carried out tests which included the testing of compositions containing α-keto-glutaric acid, 5-hydroxymethyl-furfural, and sodium selenite, an undesired reaction between the α-keto-glutaric acid and the sodium selenite occurred, resulting in the precipitation out of amorphous selenium from the composition. See page 5, lines 15 to 20 of the specification, thus sodium selenite cannot function together with α-keto-glutaric acid, 5-hydroxymethyl-furfural as a source of selenium in the treatment of tumors.

Above all, however, Applicants believe that the Examiner is interpreting the BOMMARIUS et al reference, entirely incorrectly, and the Examiner's incorrect interpretation of BOMMARIUS et al defeats his entire argument that the combination of US Patent 5,006,551 to GROKE et al with the three secondary prior art references from the literature provides a basis for the obviousness of any claim now presented.

The Examiner correctly points out that page 3197 of BOMMARIUS et al discloses N-acetyl-seleno-methionine (see compound 1c). The compound (1c) is present as a racemate and not as the N-acetyl-seleno-L-methionine. There is no disclosure of any per se activity for the racemic N-acetyl-seleno-methionine. Thus BOMMARIUS et al is silent as to any per se activity for N-acetyl-seleno-methionine in racemic form. It is only the starting material to obtain the L-selenomethionine. The reference discloses treating Compound 1c with acylase to produce compound 2c, which is L-selenomethionine (see p. 3198, fifth paragraph, line 2), which is disclosed therein in the treatment of Alzheimer's disease and Parkinson's disease, and not cancer. In addition to forming L-selenomethionine (SeMet) after the treatment with the acylase, there is a second product formed, designated as Compound 3c, which is an optically active form of N-acetyl-seleno-methionine, either N-acetyl-seleno-L-methionine or its optical antipode. Applicants cannot tell. However, there is no indication whatsoever that the optically active form of N-acetyl-seleno-methionine has the same activity as the L-selenomethionine, or for that matter any pharmaceutical activity at all. Thus BOMMARIUS et al is also silent as to any per se activity for the optically active N-acetyl-L-seleno-methionine or its optically active antipode. Applicants can find no support in the BOMMARIUS et al reference for the Examiner's statement that "Bommarius et al teaches the use of the non-proteinogenic amino acid N-acetyl-seleno-methionine in therapeutic

applications where L-selenomethionine is efficacious (p. 3197, first paragraph, compound 1-3c and p. 3198, second to last paragraph)." Applicants find no evidence in BOMMARIUS et al that N-acetyl-seleno-methionine as the L-isomer, the racemate or the D-isomer, has any activity, and for that matter Applicants find no evidence that any N-acetylated amino acid is disclosed in the reference as possessing any activity. Applicants certainly find no evidence in BOMMARIUS et al N-acetyl-seleno-L-methionine has any activity in the treatment of tumors or any ability to potentiate the activity of any other agent that has the ability to treat tumors.

The Examiner apparently believes that the disclosure in MENTER that SeMet may be effective in treating cancer together with the disclosure in BOMMARIUS et al that SeMet is used to treat Alzheimer's Disease and Parkinson's Disease renders the presently claimed invention obvious. Once again, however, Applicants find no indication in BOMMARIUS et al that the N-acetyl-seleno-L-methionine or even the racemic form thereof or the optically active antipode thereof has the same activity as L-selenomethionine, a different compound. Furthermore according to page 5, lines 7 to 14 of the specification, the N-acetyl-seleno-L-methionine is especially effective in preventing tumor angiogenesis. In the paragraph bridging pages 5 and 6 of the specification, Applicants indicate that they tested L-selenomethionine as an agent to prevent tumor angiogenesis in combination with alpha-keto-glutaric acid to see if

the L-selenomethionine could suppress angiogenic activity of tumors and found that the compound undergoes a Maillard reaction with the ketoglutaric acid, which interferes with the anti-tumor activity of the ketoglutaric acid. Therefore neither sodium selenite nor L-selenomethionine can be used in combination with α-ketoglutaric acid and 5-hydroxymethyl-furfural to suppress tumor angiogenesis. However, Applicants found no such problem with using N-acetyl-seleno-L-methionine in combination with N-acetyl-L-methionine for that purpose, as explained herein above.

Thus not only has the Examiner failed to establish that N-acetyl-seleno-L-methionine at the time of the present invention was a known anti-tumor compound, but furthermore Applicants have found in their research that N-acetyl-seleno-L-methionine is a superior anti-tumor compound to L-selenomethionine, the compound disclosed in BOMMARIUS et al as an anti-tumor compound.

Applicants also point to claims 14 and 15 directed to a method preparing the therapeutic agents according to the present invention which contain in addition to the alpha-keto-glutaric acid and the 5-hydroxymethyl-furfural, the N-acetyl-L-methionine and the N-acetyl-seleno-L-methionine in the specified mass ratio. These four component compositions are prepared in a step-wise fashion where the alpha-keto-glutaric acid is added first and then

5-hydroxymethyl-furfural, N-acetyl-L-methionine and the N-acetyl-seleno-L-methionine are added under stirring in stepwise fashion. No such process where all four components must be worked into the compositions is disclosed or suggested in GROKE et al, taken alone in combination with the three secondary references.

In view of the above, Applicants maintain that no claim now presented should be rejected as obvious in view of the cited combination of prior art references.

Applicants especially believe that new claims 23 through 26 are patentably distinguishable over the cited prior art, not only for the reasons expressed above concerning all of the claims on file, but especially because of the clinical data found in the specification on page 19 line 12 through page 28 line 19. There the composition as set forth on page 19, lines 12 through 20 was administered as an infusion to six patients suffering from advanced breast, lung, breast, uterine, esophageal, bladder or lung carcinoma. All of these patients experienced a significant improvement in their carcinoma after having received intravenous administration of the infusion set forth on page 19, lines 12 to 20, and specifically covered in claims 23 through 26, especially in claims 25 and 26. There is no suggestion of any such compositions or method of treatment or the efficacy against carcinomas in the cited combination of prior art references, and so these claims are

especially regarded as patentably distinguishable over the cited prior art.

Applicants do not believe that the Examiner's request for a terminal disclaimer to disclaim the terminal portion of any patent that may issue here beyond the expiration date of US Patent 5,006,551 because the presently claimed invention is a distinct unobvious improvement over the invention disclosed and claimed in US Patent 5,006,551. The present invention requires in the broadest sense in claim 1 that the compositions include in addition to alpha-keto-glutaric acid and a compound promoting azomethine formation selected from the group consisting of 5-hydroxymethyl furfural, dehydroascorbic acid, and vanillin, the compounds N-acetyl-seleno-L-methionine and N-acetyl-L-methionine, wherein the latter is present in excess with respect to the former. Applicants' inclusion of N-acetyl-seleno-L-methionine and N-acetyl-L-methionine in the composition results in a significant improvement in the ability of the composition to treat cancer because the N-acetyl-seleno-L-methionine disrupts the tumor angiogenesis, which contributes to a mechanism for the destruction of the tumor. See page 5, lines 7 to 14 of the English language specification. At the same time the N-acetyl-L-methionine is added in excess with respect to the amount of N-acetyl-seleno-L-methionine added to prevent the patient's body proteins from incorporating too much selenium from

the N-acetyl-seleno-L-methionine. See page 6, lines 1 through 15 of the specification.

In addition Applicants note that the expiration date of US Patent 5,006,551 appears to have passed; the expiration date appears to have been 24 January 2009, that is twenty years from the US filing date. It is absurd for the Examiner to ask the Applicants to file a terminal disclaimer to disclaim the terminal portion of any patent that may issue here beyond the expiration date of a patent that has already expired. Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

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Enclosure:
None.